The Center for Regulatory Effectiveness Invokes the Data Quality Act to Reject Published Studies on Atrazine Toxicity

Should chemical toxicity data from the peer-reviewed, published scientific literature be considered reliable enough for government risk assessors to use? The Center for Regulatory Effectiveness (CRE) says no, arguing that studies subject to rigorous peer review and published in prominent scientific journals may not be sufficiently "reliable" to be used by the government. The CRE, self-described as a regulatory watchdog group supported by business and trade associations, relies on the so-called Data Quality Act (2001), an obscure provision of a spending bill, which requires governmental agencies to develop guidelines for "ensuring and maximizing the quality, objectivity, utility, and integrity of information" they disseminate.

The issue of whether the Data Quality Act will promote greater scientific rigor or whether it will stand in the way of regulatory decision making is coming to a head as the U.S. Environmental Protection Agency (EPA) assesses atrazine, one of most widely used herbicides in the United States. Atrazine has been banned or restricted in numerous countries, and significant published literature suggests that atrazine is an endocrine disruptor (Hayes et al. 2002a, 2002b, 2003; Laws et al. 2000; Stoker et al. 1999; 2000; Tavera-Mendoza et al. 2002; Sass 2003). Nevertheless, the CRE recently objected that since

> there are no validated test methods for assessing any such effects, these pages of the Environmental Risk Assessment should be corrected to state that there is no reliable evidence that atrazine causes endocrine effects in the environment. (Frankenberry et al. 2003)

On the surface, the CRE's call for validated tests sounds innocuous, even responsible. On closer inspection, the CRE seems to be arguing that a federal agency may not base any regulatory action on scientific research unless it has been performed in accordance with a preexisting, government-approved test protocol. However, the government lacks standard protocols to assess many health effect end points and many types of studies. For example, there is no accepted government benchmark for data from epidemiologic research, for the use of pharmacokinetic models, or for most molecular methodologies. Accidental poisoning data are likewise useful to a risk assessor looking at a given chemical, but they are obviously not the result of experiments carried out under government-approved test conditions. If accepted, the CRE's arguments could jeopardize the government's ability to consider most published scientific research.

Atrazine provides an unnerving example of how the CRE approach could undermine sound policy decisions. In recent articles published in *Nature*, *Environmental Health Perspectives*, and the *Proceedings of the National Academy of Sciences*, Berkeley researcher Tyrone Hayes described a series of adverse affects on amphibian sexual development associated with atrazine exposure (Hayes et al. 2002a, 2002b, 2003). The endocrine effects reported in frogs are consistent with published studies of endocrine effects in atrazine-exposed rats, including delayed puberty in male (Stoker et al. 2000) and female (Laws et al. 2000) Wistar rat pups, prostatitis in the male pups suckling from atrazine-treated dams (Stoker et al. 1999), and reduced testosterone levels in atrazine-treated Sprague-Dawley rat pups (Friedmann 2002). All of these studies inform the U.S. EPA in its assessment of atrazine as a potential endocrine disruptor. Such studies are consistent with the Data Quality Act's goal of promoting reliable information in agency decision making, given that they were published in respected peer-reviewed journals. However, the CRE argued that these data were unreliable and should not be considered by the U.S. EPA in its atrazine assessment.

Government scientists are capable of assessing the reliability of data in order to generate scientifically defensible assessments. For example, the U.S. EPA determined that a number of studies sponsored by the atrazine manufacturer and designed to assess atrazine effects on amphibians were uninformative because of flawed study designs, insufficient statistical power, or high variability (U.S. EPA 2003).

The U.S. EPA has thus far defended its authority to consider all available data, notwithstanding these Data Quality Act objections (Frankenberry et al. 2003). The agency clearly recognizes that it needs all available data to generate a full and informed assessment of any risks. In assessing the data, the greatest consideration should be given to those data from robust and well-designed studies, particularly from studies published in the peer-reviewed scientific literature and therefore available for public scrutiny and scientific debate.

The authors are employed by an environmental nonprofit group concerned with strengthening regulation of toxic chemicals.

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Data Quality Act: Response from the Center for Regulatory Effectiveness

Sass and Devine assert that the CRE has taken a position with regard to the U.S. EPA's review of the pesticide atrazine that

> [under the new federal Data Quality standards] a federal agency may not base any regulatory action on scientific research unless it has been performed in accordance with a preexisting, government-approved test protocol

and that if accepted, this CRE position "could jeopardize the government's ability to consider most published scientific research." Sass and Devine do not fully characterize the CRE's position and the atrazine research issues, nor the U.S. EPA response.

The scientific issue raised by the CRE was the reliability of certain research suggesting that atrazine disrupts endocrine function in frogs. This research was, as Sass and Devine point out, published in peer-reviewed scientific journals. However, the research methods were novel, and attempts to reproduce the experiments in other laboratories failed to produce similar results (Carr et al. 2003). This raised a clear issue of "reliability" under the new federal data quality guidelines [Office of Management and Budget (OMB) 2001, 2002; U.S. EPA 2002]. The CRE took the position that, given this issue, the U.S. EPA could not disseminate information which concluded that atrazine had been found to cause certain endocrine effects in frogs.

The U.S. EPA (2003) agreed with the CRE position and made editorial changes to its atrazine review document to clarify that

> The revised assessment does not suggest that endocrine disruption, or potential effects on endocrine-mediated pathways, be regarded as a legitimate regulatory endpoint at this time.

The U.S. EPA (2003) went on to affirm that it was justified in considering unvalidated research published in the peer-reviewed scientific literature as a means "to identify uncertainties and additional research that may need to be conducted …."

The CRE agrees with this U.S. EPA response (U.S. EPA 2003) and has consistently taken the position that the agency must consider all peer-reviewed scientific studies when it conducts a risk assessment. However, the CRE has also taken the position that after such studies are considered, they cannot be endorsed or used in setting regulatory standards unless they meet the reproducibility and reliability standards of the data quality legislation and guidelines (OMB 2002). Publication of a research article in a peer-reviewed scientific journal does not mean that the research has been accepted as valid by the scientific community and that it should be considered reliable for regulatory purposes. Research is often published because it is believed to contain significant observations, suggest a new hypothesis, or describe potentially useful new test methods or materials. This published research then becomes subject to "postpublication peer review," in which the broader scientific community scrutinizes the methods, materials, and results and attempts to replicate or reproduce the research. Under the data quality guidelines, prepublication peer review raises only a rebuttable presumption of objectivity (which encompasses accuracy and reliability), and postpublication peer review may reveal that the published data is not of sufficient quality to be used or endorsed by a federal agency.

When novel research such as that involved here has not been validated, the CRE believes that the data quality standards of "reproducibility" and "reliability" have not been met; thus, the research results cannot be relied on or endorsed by a federal agency. An agency's assessment of such situations will necessarily involve careful review of the published peer-reviewed research, which the CRE supports.

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Risk of Arsenic Contamination in Groundwater Affecting the Ganga Alluvial Plain, India

The pandemic arsenic pollution in the Bengal Basin is caused by superimposed effects of the preferential entrapment of As in organic-rich deltaic sediments during the early- to mid-Holocene, when the sea level rose; later, severe reducing conditions developed, causing the release of As into groundwater. None of these features characterize the Ganga Alluvial Plain, where sediments in the mega fans from the Himalayan rivers that cover major parts of the alluvial plain are sandy, and associated groundwater is not reduced to the level required to cause significant mobilization of As. Chakraborti et al. (2003) recently reported severe As pollution in moderately reducing groundwater in Semaria Ojha Patti, Bihar, located within a narrow entrenched floodplain over 300 km from the head of the Ganga delta. Such local conditions are not representative of the Ganga Alluvial Plain. It is scientifically unrealistic for Chakraborti et al. (2003) to extrapolate from such local occurrences that "groundwater will be arsenic contaminated over a wide region" in the well-populated Ganga Alluvial Plain.

The Ganga delta regions are endemically prone to As contamination in groundwater. In the Bengal Basin, a rapid rise in sea level and a contemporaneously high rate of sediment discharge from fast eroding Himalayas induced delta sedimentation that occurred around 10,000–7,500 years ago (Acharyya et al. 2000; Goodbred and Kuehl, 2000). The As-bearing aquifers are mainly confined to these sediments. There is overwhelming evidence in support of reduction and ion-exchange processes that control mobilization and release of As to groundwater, although opinions differ in details of how this occurs (Acharyya 2002; Acharyya et al. 1999; Appelo et al. 2002; Bhattacharya et al. 1997; Harvey et al. 2002; McArthur et al. 2001; Nickson et al. 1998). Older tube wells are likely to establish better path flows for groundwater, enhancing the release of As to groundwater.

The source of As is dispersed in the Himalayas and in peninsular India. Chakraborti et al. (2003) misquoted our previous work (Acharyya et al. (2000) when they stated that the source is confined to "the Chotonagpur [and] Rajmahal Highlands." Adjacently exposed Bijoygarh Shale in the Kaimur Range contains pyrite with 0.26% As (Das 1977), which could be a potential source for the Semeria area.

Pyrite or arsenopyrite is absent or very rare in aquifer sediments from the Bengal Basin (Acharyya et al. 1999, 2000). The extreme rarity of pyrite in aquifers and the very low concentration of sulfate in groundwater goes against the pyrite oxidation hypothesis postulated by Chakraborti et al. (2003). Further, even if some of this pyrite is oxidized, the released As would be refixed in iron oxyhydroxide (McArthur et al. 2001).

Arsenic gets preferentially entrapped in the organic-rich, argillaceous flood-plain and delta sediments (Acharyya et al. 2000); therefore, any delta or floodplain that developed into marshland or swamp is prone to contain As-contaminated groundwater. Fe-rich groundwater (Fe > 1 mg/L) generally results from activities of Fe-reducing bacteria, which preferentially reduce least-crystalline FeOOH

phases (Lovley and Chapelle, 1995; Saunders et al. 1997). Reduction of FeOOH is common and intense in the Bengal Basin as shown by a maximum level of dissolved Fe concentration (≤ 9–36 mg/L) (Acharyya et al. 1999; British Geological Survey 1999; Nickson et al. 1998). The concentration of dissolved Fe in groundwater is generally low (< 1 mg/L) in the Ganga Alluvial Plain (Acharyya et al. 2000), thus biogeochemical conditions are generally unfavorable to trigger release of As to groundwater. However, locally, as in Semeria, where the Fe content in groundwater reaches up to 8.6 mg/L (Chakraborti et al. 2003), conditions are adequate for mobilization of As to groundwater. A poor correlation between the concentration of Fe and As in groundwater from Semaria may be caused by the presence of dissolved Fe in groundwater, which may be partly derived from the weathering of biotite, and by the variable Fe:As ratio in dissolved FeOOH (McArthur et al. 2001).

In the Ganga Alluvial Plain, the active floodplains of most of the rivers are narrow and entrenched within the broad river valleys, which are located south of the mega fan surfaces that correspond to the Himalayan rivers meeting the Ganga River. Sedimentation in these entrenched floodplains was also influenced by sea-level fluctuation during the Holocene, causing increased aggradation and formation of large fluvial lakes and swamps (Singh 2001). Semaria Ojha Patti is located about 8 km south of the Ganga River and within such an entrenched active floodplain. Its typical natural setting is thus responsible for As poisoning of tube-well water. Local As-affected pockets may also occur in northern fan areas, as recorded from the Terai region of Nepal. Future studies should focus on Holocene alluvium in entrenched floodplains and Fe-rich groundwater as the target areas for As pollution. At present, there is no evidence that As pollution is a health hazard over major parts of the Ganga Alluvial Plain.

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Risk of Arsenic Contamination in Groundwater: Response from Chakraborti et al.

We would like to reply to Acharyya and Shah's comments on our paper (Chakraborti et al. 2003). First, Acharyya and Shah should better document their statements. For example, in their discussion of the relationship of iron oxyhydroxide to arsenic, they state that

> Reduction of FeOOH is common and intense in the Bengal Basin as shown by a maximum level of dissolved Fe concentration (≤ 9–36 mg/L) (Acharyya et al. 1999; British Geological Survey 1999; Nickson et al. 1998).

In none of these articles, including Acharyya et al. (1999), did we find mention of dissolved Fe in the Bengal Basin at the value of 9–36 mg/L.

In fact, in Nickson et al.'s (1998) report on the distribution of dissolved Fe (≤ 29 mg/L) in 46 wells in Bangladesh, their Figure 1 showed that the distribution of Fe in 46 samples was between close to 0 and 29 mg/L, and most of the samples were from 1 to 10 mg/L. Also, in the British Geological Survey's (1999) report on the frequency distribution of the total dissolved Fe concentration in a regional survey of wells, the distribution was determined for 1,534 wells. Of these, 23% of samples contained < 0.3 mg/L Fe, 17% contained 0.3–1.0 mg/L, 11% contained 1.0–2.0 mg/L, 38% contained 2.0–5.0 mg/L, and 10% contained > 5.0 mg/L. Thus, we found that the available data do not support the value of 9–36 mg/L of dissolved Fe in the Bengal Basin.

In their letter, Acharyya and Shah stated that "The concentration of dissolved Fe in groundwater is generally low (< 1 mg/L) in the Ganga Alluvial Plain (Acharyya et al. 2000)." However, Acharyya et al. (2000) actually stated that

> The dissolved iron in groundwater in the Ganges basin in [Uttar Pradesh] and Bihar states in India is reported to have trace concentrations of 1.0 mg/L compared with values up to 36 mg/L in the south of West Bengal (Acharyya and others 1999) and 30 mg/L in Bangladesh (Nickson and others 1998).

Further, Acharyya et al. (1999) stated that "the groundwater of Uttar Pradesh and Bihar has trace concentrations of iron (0 to 0.7 [mg/L]) …." We have some reservations about the zero Fe concentration in 0–0.7 mg/L, and we also find an inconsistency between the "trace concentration of 1 mg/L" (Acharyya et al. 1999) and "< 1.0 mg/L" (Acharyya et al. 1999). However, it would have been helpful if Acharyya et al. (1999, 2000) had provided information about the sources of the data, how many samples were analyzed, and who analyzed them.

Without providing experimental evidence or citing other sources for data, Acharyya et al. (2000) reported that floodplains of the Jamuna and Old Brahmaputra Rivers in the Bengal Basin were free of arsenic, whereas the British Geological Survey (1999) and Chowdhury et al. (1999) established that hand tube-well water in floodplains of the Jamuna and Old Brahmaputra Rivers is contaminated with arsenic.

In their letter, Acharyya and Shah stated that "pyrite or arsenopyrite is absent or very rare in aquifer sediments from the Bengal Basin (Acharyya et al. 1999, 2000)." However, Acharyya et al. (1999) did not cite any reference of their own work or provide an analysis of bore-hole sediments to prove the absence of pyrite or arsenopyrite. Does citing these two published articles (Acharyya et al. 1999, 2000) that do not include experimental evidence prove Acharyya and Shah's comment? They seem to think so.

It is extremely interesting that in an earlier article, Achyrra (1997) stated,

> Excessive withdrawal of groundwater, [e]specially [in] summer when recharge is low, might lead to induced oxidation of aquifer material by increased access of atmospheric oxygen. Under such conditions the arsenopyrite/pyrite grains now known to be present in the aquifer material would be decomposed and arsenic will be released into the groundwater.

This is exactly what we reported earlier (Das et al. 1996).

In their letter, Acharyya and Shah comment that

> Chakraborti et al. (2003) misquoted our previous work (Acharyya et al 2000) when they stated that the source is confined to the "Chotonagpur [and] Rajmahal Highlands."

In the statement to which they refer, we (Chakraborti et al. 2003) cited both Acharyya et al. (2000) and Saha et al. (1997).

Acharyya et al. (2000) stated that

> The environment is not sufficiently reducing in Ganges floodplains upstream of Rajmahal to mobilize iron and arsenic in groundwater.

They also stated that a possible source of arsenic contamination in the Ganges basin is the Gondwana coal seams in the Rajmahal Basin, which contain up to 200 ppm arsenic. On the basis of these statements, it appears that we have not misquoted Acharyya et al. (2000).

We have been studying Bihar for the last 14 months and Uttar Pradesh for the last 5 months. This work in progress will prove that the Semria area is not an isolated case and that dissolved iron in the Ganga Alluvial Plain is not "generally low (< 1 mg/L)," as stated by Acharyya and Shah.

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Re: "Increased Concentrations of Polychlorinated Biphenyls, Hexachlorobenzenes, and Chlordanes in Mothers of Men with Testicular Cancer"

The paper by Hardell et al. (2003) is a potentially important contribution to the literature on endocrine disruption and testicular cancer. It may also have implications for other disorders of the male reproductive tract, collectively known as the testicular dysgenesis syndrome (Skakkebaek et al. 2001). It is therefore vital to establish the degree of confidence that can be placed in its findings. Issues arise in relation to the selection of cases and controls and to the selection of chemical and statistical analyses.

In a case–control study, the conventional practice is to recruit sequential cases (or a random sample) and not to select among them, other than for reasons of ability to participate, such as severity of illness or language problems. Hardell et al. (2003) stated that "… these patients did not represent all cases with testicular cancer admitted to these hospitals during this time," but they did not explain why the other cases were not included; it was not because of refusal.

To assess the extent to which the apparently nonrandom method of case selection has led to bias, the following questions need to be answered. What proportion of the total incident cases in the various participating hospitals were deemed eligible? How was eligibility determined, and by whom? From the viewpoint of the quality of the study, the important possibility is that this decision was influenced by the hypothesis under study. If, for example, cases were more likely to be included if they were particularly "interesting" for the study (e.g., because of a family background involving agriculture), the study would have been seriously biased. Hardell et al.'s (2003) statement that "no selection bias occurred because the physicians treated patients regardless of tumor type" does not address this issue.

In choosing controls, the obvious course of action is to select the control group from the same hospital(s) as the cases (sometimes with attention needed for tertiary referral processes in the case of rare diseases or those requiring specialist treatment) to try to ensure that the two groups are drawn from the same underlying population. In this study, Hardell et al. (2003) used a random sample of the Swedish population instead. This led to a geographically biased sample, unless the population density of males approximately 20–40 years of age happened to correspond with the catchment areas for testicular cancer of the hospitals used for the recruitment of cases, weighted by the number of cases for each one. This geographical bias in the match between the two samples is important for spatially varying exposures, which are likely to include at least some of the chemicals studied.

It would be possible to explore the possible geographical bias introduced by the method of selection of controls if there is information on the spatial distribution of the case and control groups. The main possibilities to compare are *a*) the proportion of the two groups who are living in rural, and especially in agricultural, areas; and *b*) their distribution across the different regions of Sweden. At least some of the chemicals studied—although possibly not dichlorodiphenyldichloroethylene (DDE) (Ekbom et al 1996)—are likely to have considerable spatial variation and to have higher concentrations in farming areas in the case of hexachlorobenzene (HCB) and the chlordanes [U.S. Environmental Protection Agency (EPA) 1997]. Origin in a farming family would be another way to examine the same thing. If such an analysis were to show that the case population is more agricultural, then it would be impossible to distinguish a real biological effect (that testicular cancer itself has "selected" farming or rural families because of exposure to these persistent organochlorine pesticides) from a selection effect created by the study design. However, if this is not the case, the findings cannot be attributed to this particular bias.

Hardell et al. (2003) gave no clear justification for their choice of these chemical and statistical analyses from among all possible endocrine disruptors (agents with estrogenic, antiestrogenic, and antiandrogenic effects) that persist in the body. HCB and *p,p′*-DDE do not seem to be controversial. Polychlorinated biphenyls (PCBs) are heterogeneous; as the authors state, some (but not others) are thought to be endocrine disruptors—but Hardell et al. (2003) provided no separate results for this group, which would be important in evaluating whether their observed effects are hormonally mediated. It would also be important to have separately-presented findings for "dioxin-like" PCBs (De Rosa et al 1997). The chlordanes are a less obvious choice, if only because they are considered to be probable human carcinogens for nonendocrine cancers (U.S. EPA 1997); therefore, it is difficult to interpret whether any observed effect on testicular cancer is or is not hormonally mediated.

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"Increased Concentrations of Polychlorinated Biphenyls, Hexachlorobenzenes, and Chlordanes": Response from Hardell and Eriksson

We thank Joffe for his interest in our paper (Hardell et al. 2003). To prevent introducing selection bias, the treating physicians asked all patients to consent to be included in a sequential way, regardless of tumor type, family history, occupation, or place of residence. We included only cases who were patients of physicians involved in the study; therefore, patients of other physicians were not included.

In epidemiologic studies, the purpose of controls is to represent the population from which the cases are recruited. In Sweden all patients with testicular cancer are referred to the university clinics in the national health system regardless of insurance or other factors. Thus, it is highly preferable to use the national population registry for recruiting controls instead of using other hospital patients, who are not representative of the whole population.

Joffe is concerned that there is a possible imbalance of agricultural or rural background among cases and controls. However, the study was balanced in this respect; only 6 cases (10%), 6 controls (10%), 7 case mothers (16%) and 8 control mothers (18%) lived in a rural area.

The persistent organochlorines analyzed in our study (Hardell et al. 2003) were chosen *a priori* because of their likelihood of being present in the food chain in Sweden. Furthermore, as we stated in our article, high concentrations were found in the food chain during the period when the cases and controls in our study were born. Regarding polychlorinated biphenyls (PCBs), 37 congeners were analyzed, but we reported only the sum of PCBs. It would be interesting to group the studied organochlorines, including the 37 PCB congeners, according to their possible hormonal activity, but at present, animal and human data are insufficient.

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